REMARKS

Claims 1-9 are pending in the instant application. Claims 1-9 have been rejected. Reconsideration is respectfully requested in light of the following remarks.

I. Rejection of Claims Under 35 U.S.C. 112, Second Paragraph

Claims 2, 6, and 8 have been rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The Examiner suggests that the limitations "testosterone derivative", "compounds that increase levels of growth hormone in blood", and "growth hormone releasing peptide mimetic compound" are unclear and indefinite as one of skill would not be able to ascertain the metes and bounds of these terms.

Contrary to the Examiner's suggestion, at page 16, lines 33-34, the term "testosterone derivative" is defined. Moreover, it would have been well-known to one skilled in the art what a testosterone derivative would be and what general structure it would have because such a term is found in the published medical literature of the time of filing of the instant specification. Even resources such as basic textbooks identified testosterone and derivatives of testosterone (see for example chapter on

Androgens in Goodman & Gilman's *The Pharmacological Basis of Therapeutics*, 2001. J.G. Hardman and L.E. Limbird (eds), 10th edition, McGraw Hill: New York, pages 1635-1648). Therefore, it was well known at the time of filing that a variety of testosterone derivatives existed and that they could be identified chemically by their structure.

Also contrary to the Examiner's suggestion, at pages 17 and 18, starting at lines 20-25 on page 17, the term "a compound that increases levels of growth hormone in blood" is defined. There, the term is found to be defined as being a growth hormone releasing agent, referred to as GRF, and is said to include substances such as GHRH, GHrelin, or a number of other growth hormone releasing peptides or peptide analogs, including hexarelin. Therefore, the specification as filed clearly defines what the scope of the compounds that would be contemplated for use in the present invention to increase levels of growth hormone in blood.

Finally, contrary to the Examiner's suggestion, the specification as filed defines the term "growth hormone releasing peptide mimetic compound", beginning at page 17, line 36., and into page 18, lines 1-7. At these pages, the idea of a peptide mimetic agent is introduced and it is defined as a hormonal effector that directly acts to release the secondary anabolic

growth factor IGF-1. The term is also defined further at page 18, lines 32-34 to include GHRP. Therefore, the specification as filed clearly defines what the scope of the compounds that would be contemplated for use in the present invention as a growth hormone releasing peptide mimetic compound.

Based on these references to information in the specification as filed, as well as information well known to one of skill in the art, Applicant believes that the requirements of 35 U.S.C. 112, second paragraph have been met and withdrawal of this rejection is respectfully requested.

II. Double Patenting

Claims 1-9 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 4-8, 10 and 13 of copending U.S. Application No. 10/464,310. The Examiner suggests that although the claims are not identical, they are not patentably distinct. Applicant respectfully disagrees, however, since the scope of the claims may change during prosecution, Applicant requests that this rejection be held in abeyance until one of the claim sets has been allowed.

III. Rejection of Claims Under 35 U.S.C. 102(b)

Claims 1, 2 and 4 have been rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 5,935,949. The Examiner suggests that this patent discloses a method of treating fibromyalgia by employing an androgen and DHEA, a testosterone derivative, and that fibromyalgia is muscle pain. Applicant respectfully disagrees with the Examiner's conclusions regarding this reference.

U.S. Patent No. 5,935,949 discloses and claims the use of an androgen, either alone or as a combination of androgens or androgen derivatives, to treat fibromyalgia and chronic fatigue syndrome which are defined in terms of their symptoms. In the case of fibromyalgia, it is defined in paragraph 2 of the Detailed Description as being a rheumatic syndrome or a "chronic widespread musculoskeletal pain syndrome with multiple tender points, fatigue, headaches, lack of restorative sleep, and numbness". Then in the data provided in the patent, several women with fibromyalgia that have been treated with an androgen are described in terms of their response to treatment. In those women, more than muscle pain is alleviated with the androgen. Other symptoms reported to be affected included energy, strength, resistance to infection, sleeplessness, anxiety, intestinal distress, and skin hypersensitivity. Nowhere does this patent

teach or suggest that the androgen is useful solely for treatment of muscle pain or muscle wasting.

Muscle pain and muscle wasting, as now claimed, are found in the specification as filed under a discussion of the issue of general muscle pain and wasting at page 16, lines 14-29. There it is clearly pointed out that apart from fibromyalgia, the instant invention has application to treatment of muscle pain. Further, the specification as filed provides data specific to the issue of muscle pain, the tender point analysis (see pages 13-15), data that was not taught in the prior art patent (5,935,949). Therefore, the present invention is a more specific assessment of the effect of androgen treatment on a specific endpoint, muscle pain. One of skill in the art would appreciate that fibromyalgia and muscle pain, more generally, are not the same condition.

MPEP 2131 states that in order to anticipate an invention the cited reference must teach each and every limitation of the claims. Clearly, the reference cited fails to teach the limitations of the claims which recite muscle pain by itself, not a more complicated disease, fibromyalgia. It is only with the specification in hand that one of skill would be aware of the application of the instant invention to treating the particular

endpoint of muscle pain. Withdrawal of this rejection is respectfully requested.

IV. Rejection of Claims Under 35 U.S.C. 103(a)

Claims 3 and 5-9 have been rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 5,935,949, in view of U.S. Patent No. 5,656,606. The Examiner suggests that it would have been *prima facie* obvious for one of ordinary skill in the art to incorporate hexarelin and IGF-1, as taught by U.S. Patent 5,656,606 (Nargund et al.), along with an androgen, taught by U.S. Patent 5.935,949 (White), as a method to treat fibromyalgia and chronic fatigue syndrome. The Examiner further suggests that one of skill would have been motivated to incorporate the additional agents with the androgen since hexarelin and IGF-1 are known to be useful to treat fibromyalgia and chronic fatigue syndrome, and at least an additive effect would be expected. Applicant respectfully disagrees with the Examiner's conclusions.

At the outset, claims 3 and 5-9 do not refer to methods of treating fibromyalgia or chronic fatigue syndrome. Therefore, the Examiner's arguments regarding these references are improper.

As discussed *supra*, U.S. Patent No. 5,935,949 (White) discloses the use of an androgen, DHEA, in an oral formulation for treatment of fibromyalgia and chronic fatigue syndrome.

Nowhere does this patent teach or suggest use of an androgen, either alone or in combination with another agent, to treat muscle pain as a general symptom, apart from fibromyalgia or chronic fatigue syndrome. In fact, this patent shows that the androgen is used successfully by itself, with no need for use of an additive agent. Therefore, there is no teaching or even motivation provided by this patent to combine another type of therapy, as claimed in the instant application.

Nargund et al. discloses the use of camphor compounds to promote release of growth hormone. Although the patent discloses use of these compounds in conjunction with compounds such as hexarelin and IGF-1, nowhere does this patent teach or suggest that the hexarelin or IGF-1 could be used without the addition of the camphor compounds of that invention. This patent only mentions the potential use of these agents in patients with fibromyalgia and chronic fatigue syndrome, yet no data are provided showing their use in such patients. Further, this patent does not teach or even suggest combination of the novel agents with others to treat these conditions. Therefore, this patent alone, or when combined with the other cited prior art patent fails to provide one of skill with any motivation to combine reference teachings. Moreover, nowhere does this patent

teach or suggest use of any compound to treat solely muscle pain or muscle wasting, apart from treatment of fibromyalgia.

Further, with respect to the Examiner's suggestion of an expected additive effect of combining hexarelin or IGF-1 with an androgen, at page 19 (lines 10-15) of the specification as filed, there is a specific discussion of the effect of growth hormone and IGF-1 in humans. It is stated that administration of growth hormone or IGF-1 reduces plasma levels of androgens in humans, citing a published paper. Therefore, contrary to the Examiner's suggestion, the combination of the two agents is not a simple issue of predictive additive effects. The combination of the two for alleviating symptoms is predicated on the ability of the androgen administered to increase serum androgen levels to a large enough extent that symptoms are reduced. As taught in the specification as filed, this is accomplished through use of the gel formulated androgen. It is the teaching of the specification as filed that makes it clear that combining the two is therapeutically desired because the addition of the androgen therapy to the growth hormone/IGF-1 therapy allows for correction of the lowered serum androgen levels that result.

MPEP 2143 states that in order to provide a motivation for combining reference teachings the prior art must suggest the desirability of the claimed invention and the mere fact that

references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination (in re Mills, 916 F.2d 680, 16 USPQ2d 1430, Fed. Cir. 1990). Even the fact that the claimed invention is within the capabilities of one of skill is not sufficient by itself to establish *prima facie* obviousness. By relying on the fact that an additive effect might be expected for the use of the two cited compounds, a specific teaching is required in the cited references to provide motivation for use of the combination. However, in this case, since it is taught that administration of growth hormone reduces serum androgen levels, one of skill would not expect that there would by any additive activity of these two treatments. It is only with the specification in hand that one understands why the combination of the two types of compounds would be desirable.

To establish a *prima facie* case of obviousness, three basic criteria must be met. MPEP 2143. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art must teach or suggest all claim limitations. The limitations of the claims, which recite a

combination of an androgen and a compound that increases levels of growth hormone in blood for treatment of muscle pain and muscle wasting, are not taught or suggested by the cited references. Either alone or when combined. The Examiner has mistakenly suggested that the claims refer to fibromyalgia treatment, which they do not. Therefore, the limitations of the claims clearly are not taught or suggested by the combination of prior art references, nor is any expectation of successful development of method such as claimed. It is only with the specification in hand that one of skill would understand that the method of the instant invention was a viable method for alleviating the specific single symptom of muscle pain in patients. Suggesting that is would be routine experimentation is not valid since the only experimentation would be clinical studies, such as the data provided in the specification as filed. Thus, the combination of prior art cited cannot render the instant claimed invention obvious. Withdrawal of this rejection is therefore respectfully requested.

V. Conclusion

Applicant believes that the foregoing comprises a full and complete response to the Office Action of record. Accordingly,

favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

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CHAPTER 59

Peter J. Snyder

Testosterone is the principal circulating androgen in men. It is secreted by the Leydig cells of the testes in response to luteinizing hormone (LH) from the pituitary gland. The varied effects of testosterone are due to its ability to act by at least three different mechanisms: by binding to the androgen receptor; by conversion in certain tissues to dihydrotestosterone, which also binds to the androgen receptor; and by conversion to estradiol, which binds to the estrogen receptor. Testosterone is responsible for male sexual differentiation in utero *and for male pubertal changes. Consequently, failure of a male fetus to secrete testosterone or to have functional androgen receptors during the first trimester results in incomplete male sexual differentiation; failure of testosterone secretion before puberty results in incomplete pubertal changes; and failure during adulthood results in a diminution, at different rates, of some aspects of virilization. In women the physiological role of testosterone and the consequences of its deficiency are not yet understood, but it is possible that it contributes to libido, energy, muscle mass and strength, and bone strength.*

Oral administration of testosterone leads to absorption into the hepatic circulation but rapid catabolism by the liver, so oral ingestion is ineffective in delivering testosterone systemically. Most attempts to devise pharmacological testosterone preparations, therefore, have involved finding ways of bypassing hepatic catabolism. The 17α-alkylated androgens can be administered orally and are not catabolized as rapidly as testosterone itself, but they tend to cause cholestasis. Esters of testosterone and a fatty acid, when injected, produce serum testosterone concentrations that remain within the normal range for one to several weeks. Transdermal preparations of testosterone deliver testosterone itself into the systemic circulation and, when applied daily, produce relatively even serum testosterone concentrations.

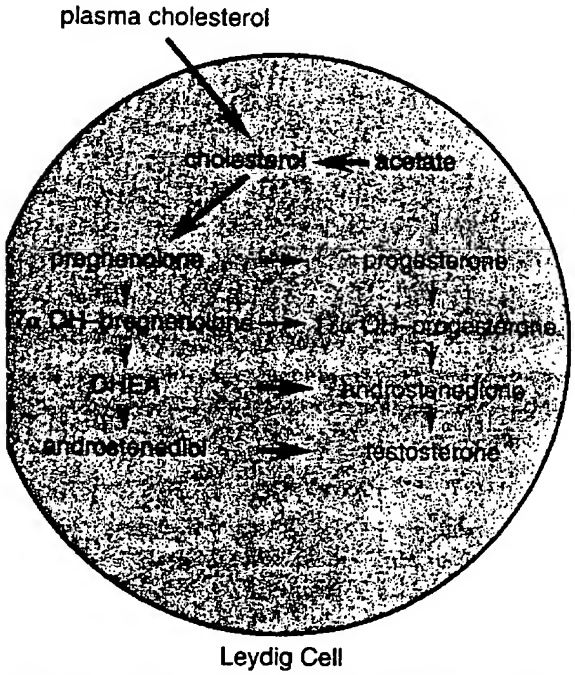
The major indication for testosterone treatment is male hypogonadism, for which a testosterone ester or transdermal preparation should be used. Treatment should be monitored for efficacy by measurement of the serum testosterone concentration and for deleterious effects by evaluating for obstruction to urine flow due to benign prostatic hyperplasia, for prostate cancer, and for erythrocytosis. Athletes have used androgens to attempt to improve their performance. Androgens have been used to attempt to develop a male contraceptive. For this purpose they have been used alone or in combination with a gonadotropin-releasing hormone (GnRH) antagonist or a progestin to suppress endogenous testosterone production and thereby spermatogenesis. The 17α-alkylated androgens are used to treat angioneurotic edema, because they stimulate C1 esterase inhibitor. Some drugs are antiandrogens that are used intentionally to inhibit undesirable effects of androgens; other drugs, used for nonhormonal purposes, have side effects as a consequence of their antiandrogenic properties. Analogs of GnRH inhibit LH secretion and thereby reduce testosterone synthesis. They are used to treat metastatic prostate cancer. A side effect of the antifungal agents of the imidazole class (see *Chapter 49*) *is direct inhibition of cortisol synthesis in the adrenal glands and testosterone synthesis in the testes. Flutamide and bicalutamide are androgen receptor antagonists that are used in combination with GnRH analogs in the treatment of metastatic prostate cancer because they block the effects of adrenal androgens. Spironolactone* (see *Chapter 29*) *is*

an aldosterone receptor antagonist and also a weak androgen receptor antagonist that causes gynecomastia when used as a diuretic in men. Finasteride is an inhibitor of the 5α-reductase enzyme, which is used to treat benign prostatic hyperplasia.

TESTOSTERONE AND OTHER ANDROGENS

ynthesis of Testosterone. In men, testosterone is the rincipal secreted androgen. The Leydig cells synthesize ıe majority of testosterone by the pathways shown in igure 59–1. In women, testosterone also is probably the rincipal androgen and is synthesized both in the cor- us luteum and the adrenal cortex by similar pathways. he testosterone precursors androstenedione and dehy- roepiandrosterone are weak androgens.

ecretion and Transport of Testosterone. The mag- tude of testosterone secretion is greater in men than women at almost all stages of life, a difference that plains almost all other differences between men and omen. In the first trimester *in utero,* the fetal testes begin



ure 59–1. Pathway of synthesis of testosterone in the dig cells of the testes.

Bold arrows indicate favored pathways. DHEA, dehydroepiandrosterone. (Adapted from Santen, 1995, with permission.)

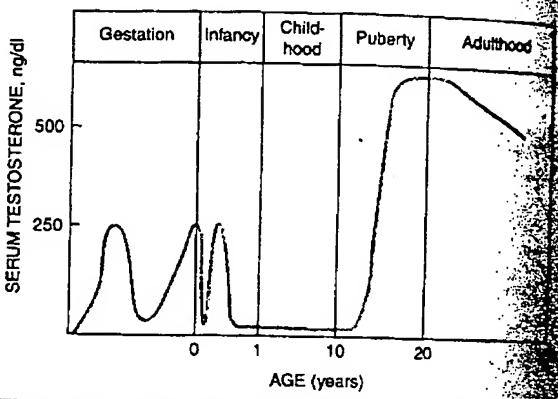


Figure 59–2. Schematic representation of the serum terone concentration from early gestation to old age.

to secrete testosterone, which is the principal fac male sexual differentiation, probably stimulated by chorionic gonadotropin from the placenta. By the ning of the second trimester, the value is close to midpuberty, about 250 ng/dl (Figure 59–2) (Dawo Saxena, 1977; Forest, 1975). Testosterone productio falls by the end of the second trimester, but by birth value is again about 250 ng/dl (Forest and Cathiard, Forest, 1975; Dawood and Saxena, 1977), possibly stimulation of the fetal Leydig cells by luteinizing mone (LH) from the fetal pituitary gland. The testo value falls again in the first few days after birth, but and peaks again at about 250 ng/dl at two to three after birth and falls to <50 ng/dl by six months, remains until puberty (Forest, 1975). During puber about age 12 to 17 years, the serum testosterone tration in males increases to a much greater degree females, so that by early adulthood the serum testo concentration is 500 to 700 ng/dl in men, compare to 50 ng/dl in women. The magnitude of the testo concentration in the male is responsible for the changes that further differentiate men from wom men age, their serum testosterone concentration ally decrease, which may contribute to other eff aging in men.

LH, secreted by the gonadotroph cells of the (*see* Chapter 56), is the principal stimulus of testo secretion in men, perhaps potentiated by follicl lating hormone (FSH), also secreted by the gonad cells. GnRH from the hypothalamus (*see* Chapter

stimulates LH secretion, and testosterone inhibits it, directly on the gonadotroph cell. LH is secreted in which occur approximately every two hours and greater in magnitude in the morning. The pulsatility is to result from pulsatile secretion of GnRH from hypothalamus. Pulsatile administration of GnRH to who are hypogonadal due to hypothalamic disease in normal LH pulses and testosterone secretion, continuous administration does not (Crowley *et al.*, Testosterone secretion is likewise pulsatile and di- with the highest plasma concentrations occurring at 8 A.M. and the lowest at about 8 P.M. The morning diminish as men age (Bremner *et al.*, 1983).

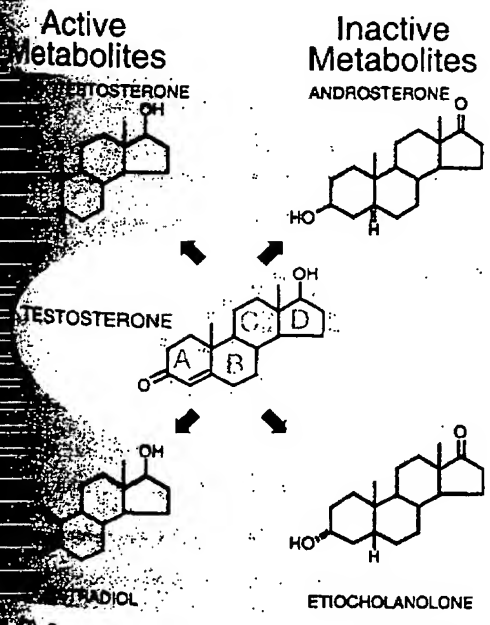
women, LH stimulates the corpus luteum (formed the follicle after release of the ovum) to secrete erone. Under normal circumstances, however, estra- and progesterone, not testosterone, are the princi- ibitors of LH secretion in women. Sex hormone globulin (SHBG) binds about 40% of circulat- tosterone with high affinity. Albumin binds almost circulating testosterone with low affinity. Approx- 2% of testosterone is unbound or free.

olism of Testosterone to Active and Inactive ounds. Testosterone has many different effects in ifferent tissues. One of the mechanisms by which ed effects are mediated is the metabolism of testos- to two other active steroids, dihydrotestosterone radiol (Figure 59–3). Some effects of testosterone appear to be mediated by testosterone itself, some by dihydrotestosterone, and some by estradiol.

The enzyme 5α-reductase irreversibly catalyzes the conversion of testosterone to dihydrotestosterone. Although both testosterone and dihydrotestosterone act *via* the same receptor, the androgen receptor, dihydrotestosterone binds with higher affinity (Wilbert *et al.*, 1983) and activates gene expression more efficiently (Deslypere *et al.*, 1992). As a result, testosterone, acting *via* dihydrotestosterone, is able to have effects in tissues that express 5α-reductase which it could not have if it were present only as testosterone. Two forms of 5α-reductase have been identified: type I, which is found predominantly in nongenital skin and the liver, and type II, which is found predominantly in urogenital tissue in men and genital skin in both men and women. The effects of dihydrotestosterone in these tissues are described below.

The enzyme complex aromatase, which is present in many tissues, especially the liver and adipose tissue, catalyzes the irreversible conversion of testosterone to estradiol. This conversion results in approximately 85% of circulating estradiol in men; the remainder is secreted directly by the testes, probably the Leydig cells (MacDonald *et al.*, 1979). The effects of testosterone thought to be mediated *via* estradiol are described below.

Testosterone is metabolized in the liver to androsterone and etiocholanolone (Figure 59–3), which are biologically inactive. Dihydrotestosterone is metabolized to androsterone, androstanedione, and androstanediol.



59–3. Metabolism of testosterone to its major active ctive metabolites.

Physiological and Pharmacological Effects of Androgens

The biological effects of testosterone can be considered by the mechanisms by which they occur and by the tissues in which they occur at various stages of life. Testosterone can act as an androgen either directly by binding to the androgen receptor or indirectly by conversion to dihydrotestosterone, which also binds to the androgen receptor as described above. Testosterone also can act as an estrogen by conversion to estradiol, which binds to the estrogen receptor (Figure 59–4).

Effects That Occur *via* the Androgen Receptor. Testosterone and dihydrotestosterone both act as androgens *via* a single androgen receptor (Figure 59–5). The androgen receptor is a member of the superfamily of nuclear receptors, which includes steroid hormone receptors, thyroid hormone receptors, and orphan receptors (*see* Chapter 2). Both testosterone and dihydrotestosterone bind to the hormone-binding domain of the androgen receptor,

Dihydrotestosterone	Testosterone	Estradiol
External genitalia (differentiation during gestation; maturation during puberty; prostatic diseases during adulthood)	Internal genitalia (Wolffian development during gestation)	Epiphyses (maturation)
Hair follicles (increased growth during puberty)	Skeletal muscle (Mass and strength increase during puberty)	? Libido
	Erythropoiesis	
	? Bone	

Figure 59–4. Direct effects of testosterone and effects mediated indirectly via dihydrotestosterone or estradiol.

allowing the ligand-receptor complex to bind, *via* the DNA-binding domain of the receptor, to certain responsive genes. The ligand-receptor complex acts as a transcription factor complex and stimulates expression of those genes (Brinkmann and Trapman, 2000).

For many years, the mechanisms by which androgens had so many different actions in so many different tissues were not understood, but recently these mechanisms have become clearer. One mechanism is the higher affinity with which dihydrotestosterone binds to and activates the androgen receptor compared to testosterone (Deslypere *et al.*, 1992; Wilbert *et al.*, 1983). Another mechanism, postulated more recently, involves transcription cofactors, both coactivators and corepressors, that are tissue specific.

The importance of the androgen receptor is illustrated by the consequences of its mutations. Predictably, mutations that either alter the primary sequence of the protein or cause a single amino acid substitution in the hormone- or DNA-binding domains result in resistance to the action of testosterone, beginning *in utero* (McPhaul and Griffin, 1999). Male sexual differentiation is, therefore, incomplete, as is pubertal development.

Another kind of mutation occurs in patients who have spinal and bulbar muscular atrophy, known as Kennedy's disease. These patients have an expansion of the CAG repeat, which codes for glutamine, at the amino terminus of the molecule (Laspada *et al.*, 1991). The result is very mild androgen resistance but progressively severe motor neuron atrophy. The mechanism by which the neuron atrophy occurs is unknown.

Yet other kinds of androgen receptor mutations may explain why prostate cancer that is treated by androgen deprivation eventually becomes androgen-independent. Prostate cancer is initially at least partially androgen-sensitive, which is the basis for the initial treatment of metastatic prostate cancer by androgen deprivation. Metastatic prostate cancer often regr... initially in response to this treatment, but then becomes ... responsive to continued deprivation. Several mutations of ... androgen receptor have been described in these patients, a... has been postulated that these mutations might allow the ... tor to respond to ligands other than androgens or to act wi... ligand activation (Visakorpi *et al.*, 1995).

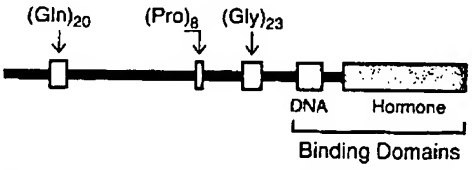


Figure 59–5. Structure of the androgen receptor.

Effects That Occur *via* the Estrogen Receptor. Th... fects of testosterone on at least one tissue are mediate... its conversion to estradiol, catalyzed by the aromatase ... zyme complex. In the rare cases in which a male does ... express aromatase (Carani *et al.*, 1997; Morishma et ... 1995) or the estrogen receptor (Smith *et al.*, 1994), ... epiphyses do not fuse and long bone growth contin... indefinitely. In addition, the patients are osteoporotic; ... ministration of estradiol corrects the bone abnormaliti... patients with an aromatase defect (Bilezikian *et al.*, ... but not an estrogen-receptor defect. There is evidence ... gesting that conversion of testosterone to estradiol m... ates male sexual behavior in rats, but similar evidence ... not yet been found in human beings.

Effects of Androgens at Different Stages of Life. *In U...* When the fetal testes, stimulated by human chorionic gona... pin, begin to secrete testosterone at about the eighth w... gestation, the high local concentration of testosterone ... the testes stimulates the nearby Wolffian ducts to differ... into the male internal genitalia: the epididymis, vas def... and seminal vesicles (George and Wilson, 1992). Further... in the anlage of the external genitalia, testosterone is con... to dihydrotestosterone, which causes the development of t... ternal genitalia: the penis, scrotum, and prostate (George ... Wilson, 1992). The increase in testosterone at the end of ... tation might result in further phallic growth.

Infancy. The consequences of the increase in testostero... cretion by the testes during the first few months of life ... yet known.

Puberty. Puberty in the male begins at a mean age ... years with an increase in the secretion of FSH and LH fro... gonadotroph cells, stimulated by increased secretion of G... from the hypothalamus. The increased secretion of FSH ... LH stimulate the testes, so, not surprisingly, the first ...

puberty is an increase in testicular size. The increase in testosterone production within the testes, along with the effect of FSH on the Sertoli cells, stimulates the development of the seminiferous tubules, which eventually produce mature sperm. Increased secretion of testosterone into the systemic circulation affects many tissues virtually simultaneously, and the changes in most of them occur gradually during the course of several years. The phallus enlarges in length and width, the scrotum becomes rugated, and the prostate begins secreting the fluid it contributes to the semen. The skin becomes coarser and oilier due to increased sebum production, which contributes to the development of acne. Sexual hair begins to grow, initially pubic and axillary hair, then hair on the lower legs, and finally other body hair and facial hair. Full development of the latter two may not occur until ten years after the start of puberty and marks the completion of puberty. Muscle mass and strength, especially of the shoulder girdle, increase, and subcutaneous fat decreases. Epiphyseal bone growth accelerates, resulting in the pubertal growth spurt, but epiphyseal maturation leads eventually to a slowing and then cessation of growth. Bone also becomes thicker. The increase in muscle mass and bone result in a pronounced increase in weight. Erythropoiesis increases, resulting in higher hematocrit and hemoglobin concentrations in men than boys or women. The larynx thickens, resulting in a lower voice. Libido develops.

Other changes also may be the result of the increase in testosterone during puberty. Men tend to have a better sense of spatial relations than do women and to exhibit behavior that is different in some ways from that of women, including being more aggressive.

Adulthood. The serum testosterone concentration and the characteristics of the adult male are maintained largely during early adulthood and midlife. One change during this time is the gradual development of male pattern baldness, beginning with recession of hair at the temples and/or at the vertex.

Two changes that can occur in the prostate gland during adulthood are of much greater medical significance. One is the gradual development of benign prostatic hyperplasia, which occurs to a variable degree in almost all men, sometimes to the degree of obstructing urine outflow by compressing the urethra as it passes through the prostate. This development is mediated by the conversion of testosterone to dihydrotestosterone within prostatic cells (Wilson, 1980). One current treatment of benign prostatic hyperplasia is based on inhibiting 5α-reductase which mediates this conversion (McConnell *et al.*, 1998), as discussed below.

The other change that can occur in the prostate during adulthood is the development of cancer. Although no direct evidence suggests that testosterone causes the disease, prostate cancer is dependent on testosterone, at least to some degree and at some time in its course. This dependency is the basis for treating metastatic prostate cancer by lowering the serum testosterone concentration (Huggins and Hodges, 1941; Iversen *et al.*, 1990).

Senescence. As men age, the serum testosterone concentration gradually declines (Figure 59–2) and the sex hormone-binding globulin concentration gradually increases, so that by age 80, the total testosterone concentration is approximately 85% and the free testosterone is approximately 40% of those at age 20 (Vermeulen *et al.*, 1981; Deslypere and Vermeulen, 1984). This fall in serum testosterone could contribute to several other changes that occur with increasing age in men, including decrease in energy, libido, muscle mass (Forbes, 1976) and strength (Murray *et al.*, 1980), and bone mineral density (Riggs *et al.*, 1982). The possibility of such a relationship is suggested by the occurrence of similar changes when men develop hypogonadism at a younger age due to known diseases, as discussed below.

Consequences of Androgen Deficiency

The consequences of androgen deficiency depend on the stage of life during which the deficiency first occurs and the degree of the deficiency.

During Fetal Development. Testosterone deficiency in a male fetus during the first trimester *in utero* can cause incomplete sexual differentiation. Testosterone deficiency in the first trimester results only from testicular disease such as deficiency of 17α-oxidoketoreductase; deficiency of LH secretion due to pituitary or hypothalamic disease deficiency does not result in testosterone deficiency during the first trimester, because Leydig-cell secretion of testosterone at that time is under the control of hCG from the placenta. Complete deficiency of testosterone secretion results in entirely female external genitalia; less severe testosterone deficiency results in incomplete virilization of the external genitalia proportionate to the degree of deficiency. Testosterone deficiency at this stage of development also leads to failure of the Wolffian ducts to differentiate into the male external genitalia, such as the vas deferens and seminal vesicles, but the müllerian ducts do not differentiate into the female external genitalia as long as testes are present and secrete müllerian inhibitory substance. Similar changes occur if testosterone is secreted normally, but its action is diminished because of an abnormality of the androgen receptor or of the 5α-reductase enzyme. Abnormalities of the androgen receptor can be quite variable. The most severe form results in complete absence of androgen action and a female phenotype; moderately severe forms result in partial virilization of the external genitalia; and the mildest forms permit normal virilization *in utero* and result only in impaired spermatogenesis in adulthood (McPhaul and Griffin, 1999). Abnormal 5α-reductase results in incomplete virilization of the external genitalia *in utero* but normal development of the male internal genitalia, which depends on testosterone *per se* (Wilson *et al.*, 1993).

Testosterone deficiency during the third trimester, due either to a testicular disease or a deficiency of fetal LH secretion, appears to have two known consequences. One is failure of the phallus to grow as much as it would normally. The result, called microphallus, is a common occurrence in boys later discovered to be unable to secre

LH due to abnormalities of GnRH synthesis. The other consequence is failure of the testes to descend into the scrotum, called cryptorchidism, also a common occurrence in boys whose LH secretion is subnormal.

Before Completion of Puberty. When a boy can secrete testosterone normally *in utero* but loses the ability to do so before the anticipated age of puberty, the result is failure to complete puberty. All of the pubertal changes described above, including those of the external genitalia, sexual hair, muscle mass, voice, and behavior, fail to occur to a degree proportionate to the abnormality of testosterone secretion. In addition, if growth hormone secretion is normal when testosterone secretion is subnormal during the years of expected puberty, the long bones continue to lengthen because the epiphyses do not close. The result is longer arms and legs relative to the trunk; these proportions are referred to as eunuchoid. Another consequence of subnormal testosterone secretion during the age of expected puberty is enlargement of glandular breast tissue, called gynecomastia.

After Completion of Puberty. When the ability to secrete testosterone becomes impaired after the completion of puberty, regression of the pubertal effects of testosterone depends on both the degree and the duration of testosterone deficiency. When the degree of testosterone deficiency is substantial, libido and energy decrease within a week or two, but other testosterone-dependent characteristics decline more slowly. Decreases in muscle mass and strength probably can be detected by testing groups of men within a few months, but a clinically detectable decrease in muscle mass in an individual does not occur for several years. A pronounced decrease in hematocrit and hemoglobin will occur within several months. A decrease in bone mineral density probably can be detected by dual energy absorptiometry within two years, but an increase in fracture incidence likely would not occur for many years. A loss of sexual hair takes many years.

In Women. Loss of androgen secretion in women results in a decrease in sexual hair, but not for many years. Androgens may have other important effects in women, and the loss of androgens (especially severe loss of both ovarian and adrenal androgens, as occurs in panhypopituitarism) may result in the loss of these effects. Testosterone preparations that can yield serum testosterone concentrations in the physiological range in women currently are being developed. The availability of such preparations will allow determining if replacement of testosterone in androgen-deficient women will improve their libido, energy, muscle mass and strength, and bone mineral density.

Therapeutic Androgen Preparations

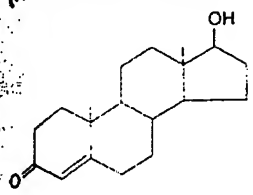
The need for a creative approach to pharmacotherapy with androgens arises from the fact that ingestion of testosterone is not an effective means of replacing testosterone deficiency. The reason is that, even though ingested testosterone is readily absorbed into the hepatic circulation, the hormone is catabolized so rapidly by the liver that it is not practical for a hypogonadal man to ingest it in sufficient amounts and with sufficient frequency to maintain a normal serum testosterone concentration. Most pharmaceutical preparations of androgens, therefore, are designed to bypass hepatic catabolism of testosterone. Another goal of androgen pharmacotherapy is to separate certain effects from others.

Testosterone Esters. Esterifying a fatty acid to the 17β hydroxyl group of testosterone creates a compound that is even more lipophilic than testosterone itself. When an ester, such as *testosterone enanthate (heptanoate)* or *cypionate (cyclopentylpropionate)* (Figure 59–6) is dissolved in oil and administered intramuscularly every two to four weeks to hypogonadal men, the ester hydrolyzes *in vivo* and results in serum testosterone concentrations that range from higher than normal in the first few days after the injection to low-normal just before the next injection (Snyder and Lawrence, 1980; Figure 59–7). Attempts to decrease the frequency of injections by increasing the amount of each injection result in wider fluctuations and poorer therapeutic effects. The undecanoate ester of testosterone (Figure 59–6), when dissolved in oil and ingested orally, is absorbed into the lymphatic circulation, thus bypassing initial hepatic catabolism. *Testosterone undecanoate* in oil also can be injected and produces stable serum testosterone concentrations for a month (Zhang *et al.*, 1998). The undecanoate ester of testosterone is not marketed in the United States.

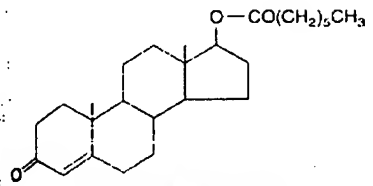
Alkylated Androgens. Several decades ago, chemists found that adding an alkyl group to the 17α position of testosterone (Figure 59–6) retarded hepatic catabolism of the molecule. Consequently, 17α-alkylated androgens do have an androgenic effect when administered orally. However, they do not appear to be as fully androgenic as testosterone itself, and they cause hepatotoxicity (Petera *et al.*, 1962; Cabasso, 1994), whereas native testosterone does not.

Transdermal Delivery Systems. Recent attempts to avoid the destructive "first pass" of testosterone through the liver have employed novel delivery systems, instead

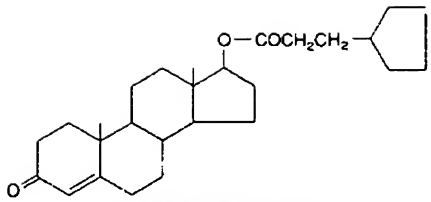
Testosterone
(HISTERONE, others)



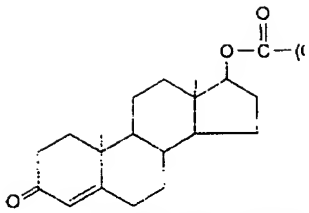
Testosterone Esters



Testosterone enanathate
(DELATESTRYL, others)

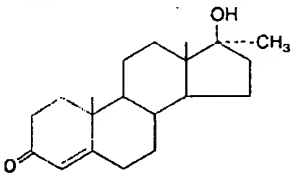


Testosterone cypionate
(DEPO-TESTOSTERONE, others)

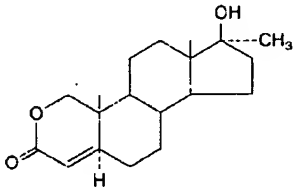


Testosterone undecanoa
(ANDRIOL)

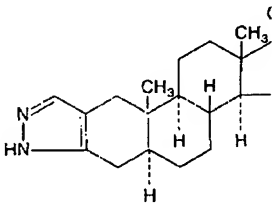
17α-Alkylated Androgens



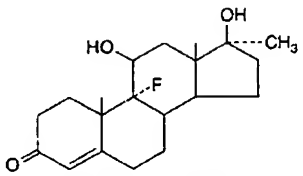
Methyltestosterone
(ORETIN METHYL, others)



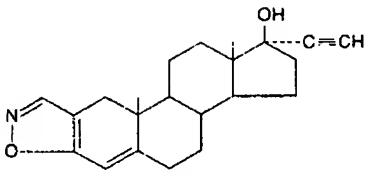
Oxandrolone
(OXANDRIN)



Stanozolol
(WINSTROL)



Fluoxymesterone
(HALOTESTIN)



Danazol
(DANOCRINE)

Figure 59–6. Structures of androgens available for therapeutic use.

of chemically modified testosterone, that release native testosterone across the skin in a controlled fashion. When these transdermal preparations are applied once a day, they result in serum testosterone concentrations that fluctuate less than when testosterone esters are administered systemically. The first such preparation was a skin patch (TESTODERM) designed to be applied to the scrotal skin (Findlay *et al.*, 1989). The rationale for that location is that the scrotal skin is so thin that sufficient testosterone can be absorbed without the need for chemicals to facilitate its absorption. Subsequent patches were d be applied to nonscrotal skin (ANDRODERM, TE TTS) and therefore employ chemicals to facilita tion (Yu *et al.*, 1997; Dobs *et al.*, 1999). A ne dermal preparation (ANDROGEL) employs a h holic gel which is applied to nonscrotal skin (W 2000). All of these preparations are applied or and all produce serum testosterone concentratic the normal range in the majority of hypogon (Figure 59–7).

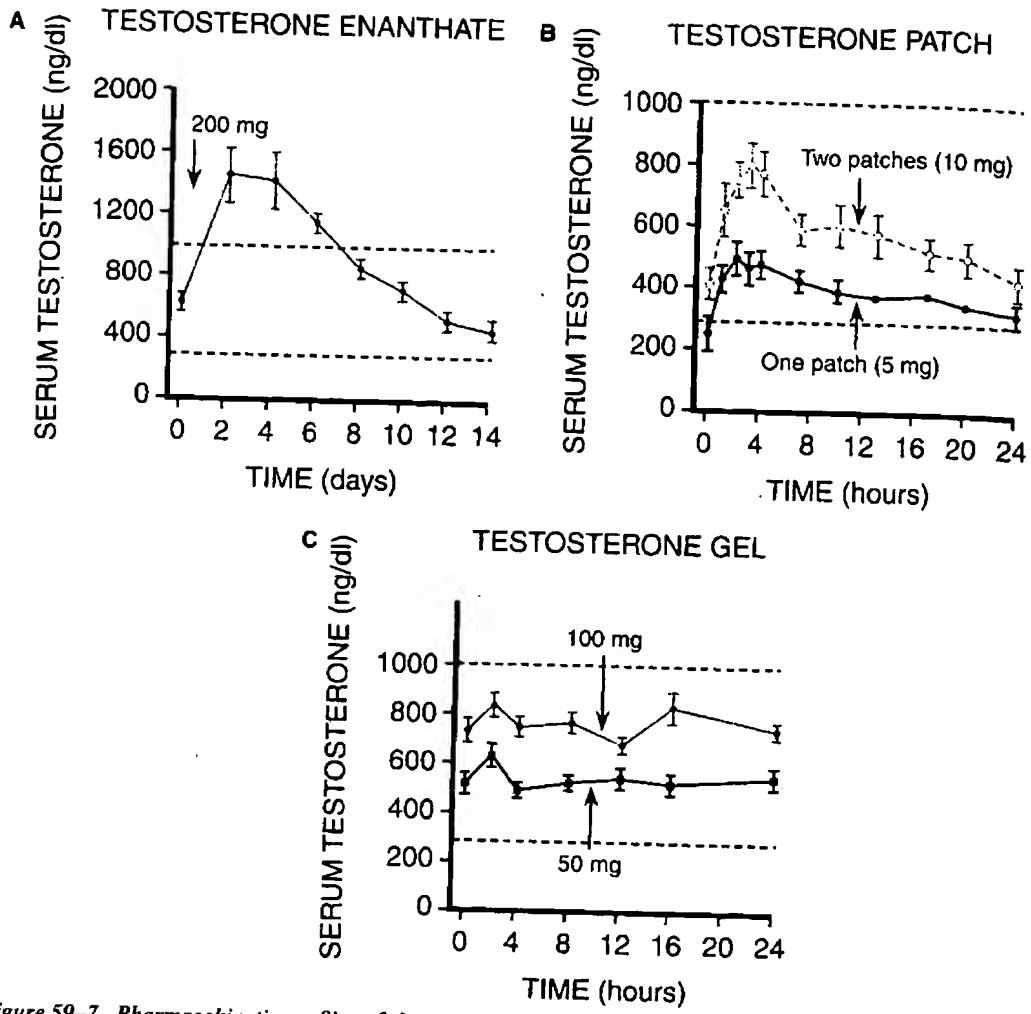


Figure 59–7. Pharmacokinetic profiles of three testosterone preparations during their chronic administration to hypogonadal men.

Doses of each were given at time 0. [Adapted from Snyder and Lawrence (1980) (A); Yu *et al.* (1997) (B); and Wang *et al.* (2000) (C).] Dashed lines indicate range of normal levels.

Attempts to Design Selective Androgens

Alkylated Androgens. Decades ago, investigators attempted to synthesize analogs of testosterone that possessed greater anabolic effects than androgenic effects compared to native testosterone. Several compounds appeared to have such differential effects, based on a greater effect on the levator ani muscle compared to the ventral prostate of the rat (Hershberger and Meyer, 1953). These compounds were called anabolic steroids, and most are 17α-alkylated androgens, described above. None of these compounds, however, has been demonstrated to have such a differential effect in human beings. Nonetheless, th[ese] have enjoyed popularity among athletes who are attempt[ing] ing to improve their performance, as described below. A[n] other alkylated androgen, 7α-methyl-19-nortestosteron[e] is poorly converted to dihydrotestosterone (Kumar *et a[l.]* 1992).

Selective Androgen-Receptor Modulators. Stimulated by [the] development of selective estrogen-receptor modulators, w[hich] have estrogenic effects in some tissues but not others, investi[ga]tors are now attempting to develop selective androgen-recep[tor] modulators (Negro-Vilar, 1999). However, the selective ef[fect] of *raloxifene* (EVISTA), the first estrogen-receptor modulator [to] be developed for clinical use, derives from its much gre[ater]

affinity for the form of estrogen receptor expressed in certain tissues, such as bone and cardiac muscle, than for the form expressed in other tissues, such as breast and uterus. Because only one form of the androgen receptor is expressed, development of compounds that have certain androgen effects but not others is based, instead, on tissue specificity of coactivators and corepressors of androgen-receptor transcriptional activity. Endogenous protein coactivators and corepressors of androgen receptor-dependent transcription have been demonstrated (Moilanen *et al.*, 1999), and a family of quinolinones that has selective androgen properties has been synthesized (Zhi *et al.*, 1999).

Therapeutic Uses of Androgens

The clearest indication for administration of androgens is testosterone deficiency in men, *i.e.*, treatment of male hypogonadism. Androgens also have been used in other situations in the past and likely will be used in yet others in the future.

Male Hypogonadism. Any of the transdermal testosterone preparations or testosterone esters described above can be used to treat testosterone deficiency. Monitoring treatment for beneficial and deleterious effects differs somewhat in adolescents and the elderly from that in other men.

Monitoring for Efficacy. The goal of administering testosterone to a hypogonadal man is to mimic the normal serum concentration as closely as possible. Therefore, measuring the serum testosterone concentration during treatment is the most important aspect of monitoring testosterone treatment for efficacy. When the serum testosterone concentration is measured depends on the testosterone preparation used. When a transdermal preparation is used, the serum testosterone concentration can be measured on any day at any time, recognizing that, when a patch is used, the peak value will be found 2 to 4 hours after application of the patch for scrotal skin (Findlay *et al.*, 1987), 2 to 4 hours after application of one patch for nonscrotal skin (TESTODERM TTS; Yu *et al.*, 1997), and 6 to 9 hours after application of another patch for nonscrotal skin (ANDRODERM; Dobs *et al.*, 1999). The nadir, before the next application, will be about 60% to 70% of the peak value (Findlay *et al.*, 1987). When the testosterone gel is used, there is no appreciable fluctuation during the course of the day, but steady-state values may not be reached for a month after the initiation of treatment. When the enanthate or cypionate esters of testosterone are administered once every two weeks, the serum testosterone concentration should be measured midway between doses. At each of these times, the serum testosterone concentration should be normal, and if not, the dosage schedule should be adjusted accordingly. If the cause of the testosterone deficiency is testicular disease, as indicated by an elevated serum LH concentration, adequacy of testosterone treatment also can be judged by its reduction to normal within two months of initiation of treatment (Snyder and Lawrence, 1980; Findlay *et al.*, 1989).

Normalization of the serum testosterone concentration results in normal virilization in men who are not normally virilized and maintenance of virilization in those who already are. Li and energy in hypogonadal men should increase within a weeks (Davidson *et al.*, 1979). Muscle mass should incr fat mass should decrease, and muscle strength should incr within a few months (Katznelson *et al.*, 1996). Bone mir density should increase to a maximum within two years (Sn *et al.*, 2000).

Monitoring for Deleterious Effects. When testosterone i is administered, as in one of the transdermal preparation as an ester that is hydrolyzed to testosterone (Caminos-Tc *et al.*, 1977), it has no "side effects" *i.e.*, no effects that end nously secreted testosterone does not have, as long as the is not excessive. Modified testosterone compounds, such as 17α-alkylated androgens, do have side effects. Even replacer of endogenously secreted testosterone levels, however, can l effects that are undesirable. Some effects occur shortly testosterone administration is initiated, whereas others usu do not occur until administration has been continued for m years. Raising the serum testosterone concentration from pr bertal or midpubertal levels to that of an adult male at any can result in undesirable effects similar to those that occur ing puberty, including acne, gynecomastia, and more aggres sexual behavior. Physiological amounts of testosterone do appear to affect serum lipids or apolipoproteins. Replacemer physiological levels of testosterone occasionally may have u sirable effects in the presence of concomitant illnesses. For ample, stimulation of erythropoiesis would increase the her ocrit from subnormal to normal in a healthy man, but w raise the hematocrit above normal in a man with a predisposi to erythrocytosis, such as in chronic pulmonary disease. Si larly, the mild degree of sodium and water retention with tes terone replacement would have no clinical effect in a hea man but would exacerbate preexisting congestive heart fail If the testosterone dose is excessive, erythrocytosis and, unc monly, salt and water retention and peripheral edema occur e in men who have no predisposition to these conditions. Whe man's serum testosterone concentration has been in the nor adult male range for many years, whether from endogenous cretion or exogenous administration, and he is over age 40, is subject to certain testosterone-dependent diseases, includ benign prostatic hyperplasia and prostate cancer, as discus above.

The principal side effects of the 17α-alkylated androg are hepatic, including cholestasis and, uncommonly, peli hepatis, blood-filled hepatic cysts. Hepatocellular cancer been reported rarely, so that an etiologic link is uncert The 17α-alkylated androgens, especially in large amounts, n lower serum high-density-lipoprotein cholesterol.

Monitoring at the Anticipated Time of Puberty. Adm istration of testosterone to testosterone-deficient boys the anticipated time of puberty should be guided by considerations above, but also by the fact that testosterc accelerates epiphyseal maturation, leading initially tc growth spurt but then to epiphyseal closure and perm nent cessation of linear growth. Consequently, the hei and growth-hormone status of the boy must be consider Boys who are short because of growth-hormone deficien

should be treated with growth hormone before their hypogonadism is treated with testosterone.

Male Senescence. Preliminary evidence suggests that increasing the serum testosterone concentration of men whose serum levels are subnormal for no reason other than their age will increase their bone mineral density and lean mass and decrease their fat mass (Snyder *et al.*, 1999a; Snyder *et al.*, 1999b). It is entirely uncertain at this time, however, if such treatment will worsen benign prostatic hyperplasia or increase the incidence of clinically detectable prostate cancer.

Female Hypogonadism. It remains to be determined if increasing the serum testosterone concentrations of women whose serum testosterone concentrations are below normal will improve their libido, energy, muscle mass and strength, and bone mineral density.

Enhancement of Athletic Performance. Some athletes take drugs, including androgens, to attempt to improve their performance. Because androgens taken for this purpose usually are taken surreptitiously, information about their possible effects is not as good as that for androgens taken for treatment of male hypogonadism.

Kinds of Androgens Used. Virtually all androgens produced for human or veterinary purposes have been taken by athletes. When use by athletes began more than two decades ago, 17α-alkylated androgens and other compounds that were thought to have greater anabolic effects than androgen effects relative to testosterone (so-called "anabolic steroids") were used most commonly. Because these compounds can be detected readily by organizations that govern athletic competitions, preparations that increase the serum concentration of testosterone itself, such as the testosterone esters or human chorionic gonadotropin, have increased in popularity. Testosterone precursors, such as androstenedione and dehydroepiandrosterone (DHEA), also have increased in popularity recently because they are not regulated by national governments or athletic organizations.

Efficacy. Most studies of the effects of pharmacological doses of androgens on muscle strength have been uncontrolled, but in one study, testosterone or placebo was administered in a double-blind fashion. In that study, 43 men were randomized to one of four groups: strength training exercise with either 600 mg of testosterone enanthate once a week (more than six times a replacement dose) or placebo for testosterone; or no exercise with either testosterone or placebo. The men who received testosterone experienced an increase in fat-free mass and muscle strength compared to those who received placebo treatment, and the men who exercised simultaneously experienced even greater increases (Bhasin *et al.*, 1997).

In another double-blind study, men who took 100 mg of androstenedione three times a day for eight weeks did not experience an increase in muscle strength compared to men who took placebo. Failure of this treatment to increase muscle strength is not surprising, because it also did not increase the mean ... testosterone concentration (King *et al.*, 1999).

Side Effects. Some side effects of taking pharmacological ... of androgens occur with all androgens and all circumstances ... others occur only with certain androgens or in certain circumstances. All androgens suppress gonadotropin secretion ... taken in high doses and thereby suppress endogenous ... ular function. The result is a decrease in both endoge... testosterone and sperm production, resulting in diminished ... tility. If administration continues for many years, testicular ... may diminish. Testosterone and sperm production usually ... turn to normal within a few months of discontinuation but ... take longer. High doses of androgens also causes erythrocy... (Drinka *et al.*, 1995).

Androgens that can be converted to estrogens, such ... testosterone itself, cause gynecomastia when administered ... high doses. Androgens whose A ring has been modified so ... it cannot be aromatized, such as dihydrotestosterone, do ... cause gynecomastia even in high doses.

The 17α-alkylated androgens are the only androgens ... cause hepatotoxicity, as discussed above. These androgens ... appear to be much more likely than others, when administered ... in high doses, to affect serum lipid concentrations, specifically ... to decrease high-density-lipoprotein (HDL) cholesterol and ... crease low-density-lipoprotein (LDL) cholesterol. Other side ... fects have been suggested by many anecdotes but have not ... confirmed, including psychological disorders and sudden ... due to cardiac disease, possibly related to changes in lipids ... to coagulation activation.

Certain side effects occur specifically in women and ... dren. Both experience virilization, including facial and ... hirsutism, temporal hair recession in a male pattern, and ... Boys experience phallic enlargement and women clitoral ... largement. Boys and girls whose epiphyses have not yet ... experience premature closure and stunting of linear growth.

Male Contraception. Attempts currently are being made ... develop androgens alone or in combination with other drugs ... male contraceptives based on their ability to inhibit secretion ... of LH by the pituitary, which in turn decreases endogenous ... testosterone production. Because the concentration of testosterone within the testes is normally approximately one hundred times that in the peripheral circulation, and that concentration is necessary for spermatogenesis, suppression of endogenous testosterone production greatly diminishes spermatogenesis. Potential use of testosterone alone to suppress spermatogenesis has ... ever, required administration of approximately twice as much ... testosterone enanthate as would be used for physiological replacement, and even then spermatogenesis was not entirely suppressed in all men (WHO Task Force for the Regulation of Fertility, 1996). Other early attempts to suppress spermatogenesis employed a GnRH antagonist to suppress LH secretion ... combined with a physiological dose of testosterone to maintain a normal serum testosterone concentration (Pavlou and ... 1991). That combination is not practical for widespread use ... because existing GnRH antagonists require daily injection ... have strong histamine-releasing properties. A more promising approach is the combination of a progestin with a physiological dose of testosterone to suppress LH secretion and spermatogenesis but provide a normal serum testosterone concentration (... *et al.*, 1996). Androgens currently being tested as part ...

contraceptive regimens include an injectable form of testosterone undecanoate, which appears to produce a relatively stable serum testosterone concentration for a month (Zhang *et al.*, 1999), and 7α-methyl-19-nortestosterone, a synthetic androgen that cannot be metabolized to dihydrotestosterone (Cummings *et al.*, 1998).

Catabolic and Wasting States. Testosterone, because of its anabolic effects, has been used in attempts to ameliorate catabolic and muscle-wasting states, but it has not been effective in most of these states. One exception is in the treatment of muscle wasting associated with acquired immunodeficiency syndrome (AIDS), which is accompanied by hypogonadism. Treatment of men with AIDS-related muscle wasting and subnormal serum testosterone concentrations increases their muscle mass and strength (Bhasin *et al.*, 2000).

Angioneurotic Edema. Chronic androgen treatment of patients with angioneurotic edema effectively prevents attacks. The disease is caused by hereditary impairment of C1-esterase inhibitor or acquired development of antibodies against it (Cicardi *et al.*, 1998). The 17α-alkylated androgens, such as stanozolol and danazol, act by stimulating the hepatic synthesis of the esterase inhibitor. In women, virilization is a potential side effect. In children virilization and premature epiphyseal closure prevent chronic use of androgens for prophylaxis, although they are used occasionally for treatment of acute episodes.

Blood Dyscrasias. Androgens once were employed to attempt to stimulate erythropoiesis in patients with anemias of various etiologies, but the availability of erythropoietin has supplanted this use. Androgens, such as danazol, still are used occasionally as adjunctive treatment for hemolytic anemia and idiopathic thrombocytopenic purpura that are refractory to first-line agents.

ANTIANDROGENS

Because certain effects of androgens are undesirable, at least under certain circumstances, agents have been developed specifically to inhibit androgen synthesis or effects. Other drugs, originally developed for other purposes, have been found to be antiandrogens. When these drugs are used for their originally intended purposes, their antiandrogenic effects can be undesirable side effects, but some are used intentionally as antiandrogens.

Inhibitors of Testosterone Synthesis. Analogs of GnRH effectively inhibit testosterone synthesis by inhibiting LH secretion. GnRH antagonists block the action of endogenous GnRH at the gonadotroph cell's GnRH receptor. Antagonists that are currently available require daily injection and have significant histamine-releasing properties, so their therapeutic use is not practical. GnRH "superactive" analogs, given repeatedly, down-regulate the GnRH receptor and currently are available for treatment of metastatic prostate cancer (*see* Chapter 56).

Some antifungal drugs of the imidazole family, such as ketoconazole (*see* Chapter 49), block the synthesis of steroids, including testosterone and cortisol (Feldman 1986). Because of the inhibition of cortisol and hepatotoxicity, these drugs are not generally useful to inhibit androgen synthesis intentionally.

Inhibitors of Androgen Action

These drugs act by inhibiting the binding of androgens to the androgen receptor or by inhibiting 5α-reductase.

Androgen Receptor Antagonists. ***Flutamide and Bicalutamide.*** These are relatively potent androgen receptor antagonists which are limited in their effectiveness when used alone, because increased secretion of LH stimulates higher serum testosterone concentrations. They are used primarily in conjunction with a GnRH analog in the treatment of metastatic prostate cancer (*see* Chapter 52). In this situation, they block the action of adrenal androgens which are not inhibited by GnRH analogs. Survival rates in groups of patients with metastatic prostate cancer treated with a combination of a GnRH agonist and either *flutamide* (EVLEXIN) or *bicalutamide* (CASODEX) are similar to each other (Schellhammer, Sharifi, *et al.*, 1995) and survival rates in those treated by castration (Iversen *et al.* 1990). Bicalutamide is replacing flutamide for this purpose, because it appears to have less hepatotoxicity and needs to be taken only once a day instead of three times a day. Flutamide also has been used to treat hirsutism in women, and it appears to be as effective as any other treatment (Venturoli *et al.*, 1999), but its hepatotoxicity cautions against its use for this cosmetic purpose.

Spironolactone. *Spironolactone* (ALDACTONE; *see* Chapter 2) is an inhibitor of aldosterone which also is a weak inhibitor of the androgen receptor and a weak inhibitor of testosterone synthesis. When it is used for treatment of fluid retention and hypertension in men, gynecomastia is a common side effect (Caminos-Torres *et al.*, 1977). Conversely, it can be used intentionally in women to treat hirsutism, for which it is approved by the U.S. Food and Drug Administration and is moderately effective (Cumming *et al.*, 1982), but it may cause irregular menses.

Cyproterone Acetate. Cyproterone acetate is a progestin and a weak antiandrogen by virtue of binding to the androgen receptor. It is moderately effective in reducing hirsutism alone or in combination with an oral contraceptive (Venturoli *et al.*, 1999), but it is not approved for use in the United States.

Selective Androgen-Receptor Antagonists. A group of quinoline derivatives has been developed that act as antagonists at the androgen receptor in rat prostate glands but not in the pituitary. Analogous effects have not yet been demonstrated in humans beings, but these compounds suggest the possible development of selective androgen-receptor antagonists.

5α-Reductase Inhibitors. *Finasteride* (PROSCAR) is an antagonist of 5α-reductase, especially the type II, so it blocks the conversion of testosterone to dihydrotestosterone, especially in the male external genitalia. It was developed as a treatment for benign prostatic hyperplasia, and it is approved in the United States and many other countries for this purpose. When it is administered to men with moderately severe symptoms due to obstruction of urinary tract outflow, serum and prostatic concentrations of dihydrotestosterone decrease, prostatic volume decreases, and urine flow rate increases (McConnell *et al.*, 1998). Impotence is a well-documented although infrequent side effect of this use, although the mechanism is not understood. Finasteride also is approved for use in the treatment of male pattern baldness under the trade name PROPECIA, even though that effect is presumably mediated *via* the type I enzyme. It appears to be as effective as flutamide and the combination of estrogen and cyproterone in the treatment of hirsutism (Venturoli *et al.*, 1999), but is not approved in the United States for this purpose.

For further discussion of disorders of the testes and of sexual differentiation, *see* Chapters 336 and 339 in *Harrison's Principles of Internal Medicine*, 14th ed., McGraw-Hill, New York, 1998.

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